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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/630,968	ROSSI ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,17 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2010 has been entered.

Status of Claims

Claims 1-9, 17, and 19-23 are pending and under examination on the merits in the instant case.

Response to Arguments

Applicant's arguments with respect to claims 1-9, 17, and 19-23 filed with the RCE have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

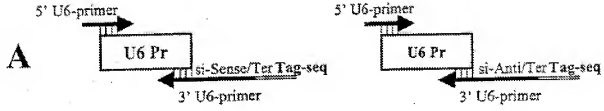
Claims 1-9, 17, and 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claims 2-9, 17, and 19-23 depend from claim 1. Claim 1 comprises three method steps, wherein the first step is treating one strand of a double-stranded mammalian promoter sequence with an oligonucleotide primer that is complementary to the 5' end of the "one strand" of the double-stranded mammalian promoter sequence, and the second step is treating the "other strand" of the double-stranded mammalian promoter sequence with an oligonucleotide primer (termed "second primer") that is complementary to the 3' end of the "other strand" of the double-stranded mammalian promoter sequence, "wherein the second primer comprises a sequence which is complementary to a sequence encoding either a sense sequence of an siRNA molecule or an antisense sequence of an siRNA molecule, along with a terminator sequence".

First, claim 1 does not distinctly claim what each of the "one stand" and "the other strand" refers to in terms of the "double-stranded mammalian promoter sequence". The unclear claim language renders the claimed method steps indefinite because of the following reasons:

If the "one strand" in the first method step is the mammalian promoter sequence in a sense orientation in the 5' end to the 3' end direction, "the other strand" in the second method step has to be the mammalian promoter sequence in an antisense orientation. Now, the second method step requires that the oligonucleotide primer ("second primer") is not only complementary to the 3' end of the "antisense" strand of the mammalian promoter sequence but also complementary to either the sense strand or the antisense strand sequence of an siRNA

molecule as well as the terminator sequence. Hence, the "second primer" must possess three binding/hybridization nucleotide sequences, binding to the 3' end of the "antisense" strand of the promoter, a strand of an siRNA sequence, and a terminator sequence. However, if the "second primer" is designed to be complementary to the 3' end of the "antisense" strand of the promoter sequence, it is impossible for the same "second primer" to be complementary to an siRNA sequence and a terminator sequence without being complementary to the 5' end of the "antisense" strand of the promoter sequence, assuming that the siRNA sequence and the terminator sequence are placed downstream from the double-stranded promoter sequence. Note that the "3' U6-promoter" depicted in the drawings in Figures 1A-1D in fact is designed to be complementary to the 5' end of the antisense strand of the U6 promoter sequence. Note that the antisense strand (or the lower strand) is written from 3' end (left) to the 5' end (right) direction. Hence, the drawings in Figures 1A-1D depict a method using a "5' U6-primer" that is complementary to the 5' end of the "sense" strand of the U6 promoter sequence and a "3' U6-promtoer" that is complementary to the 5' end of the "antisense" strand of the U6 promoter sequence. See Figure 1A as shown below:



As such, one of ordinary skill in the art cannot arrive at the claimed methods if the "one strand" and "the other strand" are not distinctly claimed, and if the "second primer" is complementary to the 3' end of the antisense strand sequence of the double-stranded promoter sequence. For examination purpose, the primer recited in the first method step will be interpreted

to mean that it is complementary to the 5' end of the sense strand of the promoter sequence and the "second primer" will be interpreted to mean that it is complementary to the 5' end of the antisense strand of the promoter sequence placed in an antisense orientation (direction), in light of Figure 1A.

Second, claim 1 fails to particularly claim appropriate method steps/materials for producing an expression cassette encoding a double-stranded siRNA sequence. Note that the second and third method steps require the "second primer" whose portion is complementary to either the sense strand or the antisense strand sequence. Hence, the primer amplifies in an amplification reaction only one of the two strands, not both. In addition, the third method step expressly recites that the amplified product contains "a sequence encoding either the sense sequence of the siRNA molecule or the antisense sequence of the siRNA molecule", not both the sense strand and the antisense strand of the siRNA molecule, which is defined to be double-stranded. See paragraph 0004 of the instant specification: "Double-stranded RNAs are processed into 21 to 23 nucleotide (nt) fragments known as siRNA (small interfering RNAs)." Also note that the claims are drawn to a method for "producing a mammalian promoter-containing siRNA expression cassette". Hence, the methods of claims 1-9, 17, and 19-23 should produce a mammalian promoter-containing "double-stranded" siRNA expression cassette in light of the disclosure of the instant specification. However, the method steps claimed in the instant case are designed to produce a cassette containing only an antisense strand of an siRNA molecule or a cassette containing only a sense strand of an siRNA molecule. Thus, claim 1 and its dependent claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. For examination purpose, the methods in the instant case will be

interpreted to mean method for producing either the sense strand of an siRNA molecule or an antisense strand of an siRNA molecule, such that only one of the two strands is expressed when transfected (for example see claim 17) to a mammalian cell.

Claim 1 recites the limitation "said primers" in line 13. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 recites the limitation "the extension products" in line 14. There is insufficient antecedent basis for this limitation in the claim. Note that it is unclear what is encompassed by the limitation "the extension products" in line 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

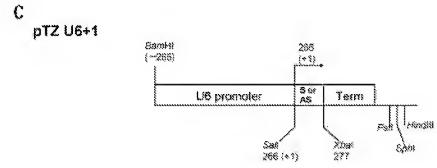
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 17, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Nature Biotechnology, 2002, 19:500-505) in view of MacFerrin et al. (PNAS, 1990, 87:1937-1941), Lindermann et al. (US 5,958,738), Livache et al. (US 5,795,715, citation of record).

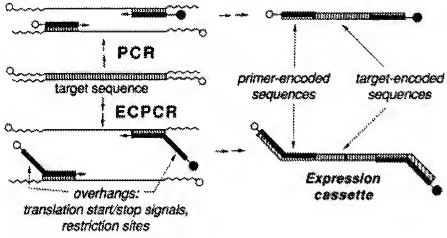
Lee et al. teach that one can construct a U6 promoter-containing expression cassette for expressing the sense strand of an siRNA molecule or the antisense strand of an siRNA molecule, wherein the siRNA sequence is operably placed downstream from the human U6 snRNA promoter and upstream from the termination signal sequence (a short stretch of six thymidines). See Figure 1C as shown below:



Lee et al. teach that the siRNA sequence (sense strand or antisense strand sequence) is inserted into a transcriptional cassette, which is "pTZ U6+1" via restriction enzyme-based digestion and ligation methods. Thus, Lee et al. teach a cloning-based method for producing a promoter-containing siRNA expression cassette. They also teach that one can transfect the U6 promoter-containing siRNA expression vector into mammalian cells. They teach that one can use "siRNA constructs targeted to different sites" in the target sequence, thereby screening for a

potent target site for siRNA constructs. See page 504, left column. They also teach that one can use EGFP sequence to detect or tag siRNA sequences. Lee et al. do not teach that the siRNA expression cassette is produced by a PCR-based amplification method.

MacFerrin et al. teach a PCR amplification-based method for producing a promoter-containing, double-stranded oligonucleotide expression cassette, termed "expression-cassette polymerase chain reaction (ECPCR)" as depicted in Figure 1 shown below:



MacFerrin et al. teach that ECPCR comprises a pair of primer oligonucleotides, one hybridizing to and encoding the expression cassette nucleotide sequence in the 3' region (e.g., transcription termination signal sequence) and the other hybridizing to and encoding the expression cassette nucleotide sequence in the 5' region (e.g., transcription start sequence; promoter sequence). They teach that the primer oligonucleotides in the ECPCR protocol also contain restriction enzyme site sequences to introduce restriction enzyme sites into the expression cassette, thereby producing an expression cassette that is "suitably equipped for cloning." See page 1937. They teach that the "use of PCR to add new sequence information concomitant with amplification has found wide applicability in recombinant DNA technology,

and the ECPCR protocol is representative of such methods. Particularly intriguing is the demonstration that the T7 promoter sequence can be added to target DNA in order to facilitate sequence analysis; indeed, those results indicate that it should be possible to engineer T7-based overproduction systems using an ECPCR-like strategy in combination with previously described vectors…The length of noncomplementary sequences added during ECPCR is primarily limited not by PCR amplification, but by the size limitation of automated DNA synthesis (routinely >100 nucleotides); hence, the potential exists to incorporate additional sequence motifs (e.g., synthetic promoters or periplasmic signal sequences) during the ECPCR procedure." See page 1940, right column.

Lindermann et al. teach that it is within the skill of the art to prepare primers capable of annealing to primer binding sites. They teach that one can make and use phosphorylated primer oligonucleotides. They teach that 5' end modifications on the primer oligonucleotides render the primer oligonucleotides resistant to a 5'-specific exonuclease. See column 18.

Livache et al. teach that the principle of PCR is "well known" (see column 5) and that one can use PCR to produce double-stranded nucleic acid, for example, a double-stranded promoter sequence (see column 2: "Promoter is understood to mean any double-stranded sequence of DNA comprising a binding site recognized by a DNA-dependent RNA polymerase") such that "a template DNA proved with promoters can be specifically produced, from a nucleic acid sample, by a technique such as PCR, using primers containing promoter sequences for the amplification of the target sequence." See column 6, lines 12-15.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the expression cassette comprising the U6 promoter-siRNA sequence-

termination signal sequence insert of Lee et al. by utilizing the ECPCR protocol of MacFerrin et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to produce an siRNA sequence expression construct in a more facile manner without the labor and time involved with the restriction enzyme-based cloning and subcloning methods of Lee et al., because the ECPCR procedure of MacFerrin et al. was suggested to be based on a PCR primer-based amplification method that allows incorporation of additional nucleotide sequences into an expression cassette during PCR amplification, thereby enabling a production of a desired expression cassette comprising a desired promoter sequence, a desired nucleotide insert sequence, a desired stop sequence, and desired restriction enzyme site sequences without the need to perform the laborious cloning and subcloning/ligation procedures. Note that MacFerrin et al. taught that ECPCR "facilitates overproducer construction by effecting site-specific replacement of the 5' and 3' ends of the gene with expression sequences derived from synthetic oligonucleotides." and that "ECPCR also takes advantage of the now-routine ability to introduce restriction sites via the polymerase chain reaction, yielding gene expression cassettes that are suitably equipped for cloning." See page 1937. As such, given the advantages associated with the alternative methodology (ECPCR) for producing an expression cassette and further given the fact that "use of PCR to add new sequence information concomitant with amplification has found wide applicability in recombinant DNA technology, and the ECPCR protocol is representative of such methods." (see page 1940 of MacFerrin et al.), one of ordinary skill in the art would have been motivated to use the ECPCR methodology of MacFerrin et al. to produce the U6 promoter-based siRNA expression cassette of Lee et al. Further, since the target-

specific siRNA sequence is the variable that is "added" into an expression cassette as "new sequence information" when making expression cassettes encoding different siRNA sequences, it would have been obvious to one of ordinary skill in the art to make a pair of PCR primers that hybridize with the constant nucleotide sequence, which is the human U6 snRNA promoter sequence recognized in the art to be suitable for transcribing siRNA sequences as taught by Lee et al. Since all skills, knowledge, and information necessary to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time the invention was made, in particular those pertaining to designing and making suitable PCR primers that can effectively amplify a desired expression construct (e.g., "PCR permits targeted amplification of DNA sequences."; "The specific segment of DNA amplified in PCR is dictated by the choice of base-pairing sites for oligonucleotide primers."; "DNA sequences of the primers are incorporated entirely into the product DNA"; see page 1937 of MacFerrin et al. See also column 18, lines 5-9 of Lindermann et al., which teach that "It is within the skill of the art to prepare either type of [phosphorylated or non-phosphorylated] primer by automated synthesis."; see column 5 of Livache et al., which teaches that PCR is "well known" and see column 6 that teaches that one can use PCR primers containing promoter sequences), the claims taken as a whole would have been prima facie obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita (AU1637, Acting SPE) can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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